CONSIDERED: /ADS/

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Case No. 00-505-B)

In the Application of:	)	
	)	
Progulske-Fox *et al.*	)	
	)	**Examiner: Steele**
Serial No.: 09/980,845	)	
	)	**Group Art Unit: 1639**
Filing Date: April 8, 2002	)	
	)	**Confirmation No. 3701**
For: Microbial Polynucleotides Expressed	)	
During Infection of a Host	)	
	)	

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

Dear Sir:

1. I, Martin Handfield, am an inventor of the above-mentioned application. Oragenics, Inc. is the entire assignee of the above-mentioned application. I have been Oragenics' Director of Research and Development since January of 2009. I previously spent 13 years of service at the University of Florida, where I co-founded *ivi*Gene Corp. and Epicure Corp. to commercialize IVIAT and related technologies. IVIAT (*In vivo* induced antigen technology) is a novel technology that can quickly and easily identify *in vivo* induced genes of bacteria in human infections, without the use of animal models. This technology facilitates the discovery of new targets for vaccines, antimicrobials and diagnostic strategies in a wide range of microbial pathogens. I am currently on a leave of absence from the University of Florida where I served as a Tenured Associate Professor at the Center for Molecular Microbiology and the Department of Oral Biology in the College of Dentistry. In the past decade, I was an inventor of four patents, and authored more than 40 publications and book chapters with a focus on infectious diseases, transcriptomics, proteomics and molecular microbiology. My articles have been featured in some of the most prominent journals in the field including the Proceedings of the National Academy of Sciences (PNAS), Trends in Microbiology, Molecular Microbiology, Infection and Immunity, Cellular Microbiology and Periodontology 2000. I received my undergraduate degree in biochemistry, and my MS and PhD in Microbiology and Immunology from

the Université Laval College of Medicine in Canada. I did my postdoctoral training at the University of Florida under the mentorship of Oragenics' Chief Scientific Officer, Dr. Jeffrey Hillman. I have attached a copy of a biographical sketch.

2. The specification of the instant application terms the methods of the invention as "IVIAT methodology." *See* specification page 10, lines 10-15. The term "IVIAT methodology" has also been recognized in the art as the name of methods as described in the instant invention.

3. Over 20 scientific papers have been published that report the successful use of the IVIAT methodology of the claims to isolate polynucleotides of microbes that are expressed only *in vivo*. *See* Appendix A to this Declaration. The IVIAT methods of the invention have been used by the those of skill in the art to isolate polynucleotides of microbes including, *e.g.*, *Vibrio anguillarum, Porphyromonas gingivalis, Streptococcus suis, Brucella abortus, Salmonella enterica, Edwardsiella tarda, Paracoccidiodes brasileinsis, Borrelia burgdorferi, Mycobacterium tuberculosis, Bacillus anthrasis, Tannerella forsythia,* group A *Streptococcus, Escherichia coli, Actinobacillus actinomycetemcomitans, Vibrio vulnificus, Vibrio choerae.* *See* Appendix A to this Declaration. These polynucleotides are expressed by a microbe only *in vivo* as taught by the instant specification.

4. Those of skill in the art have also recognized that the polynucleotides and the polypeptides expressed from the polynucleotides discovered using IVIAT are important vaccine targets and diagnostic targets, just as described by the specification.

5. For example, Gu *et al.* teaches that the "the proteins identified using IVIAT may be useful potential vaccine candidates or virulence markers." *See* Gu *et al.* Use of *in vivo*-induced antigen technology (IVIAT) for the identification of *Streptococcus suis* serotype 2 *in vivo*-induced bacterial protein antigens. BMC Microbiol. 9:201 (copy of abstract attached). Kudva *et al.* teaches that "Because ivi[at] proteins are expressed in response to specific cues during infection and might help pathogens adapt to and counter hostile *in vivo* environments, those identified in this study are potential targets for drug and vaccine development. Also, such proteins may be exploited as markers of O157 infection in stool specimens." Kudva *et al.*, Use of *in vivo*-induced antigen technology for identification of Escherichia coli O157:H7 proteins expressed during human infection. Infect Immun. 73:2665-79 (2005) (copy of abstract attached). Zou *et al.* teaches that "[t]he identification of ivi[at] genes in *V. anguillarum* M3 sheds light on understanding the bacterial pathogenesis and provides novel targets for the development of new vaccines and diagnostic reagents." Zou *et al.*, Screening of genes expressed *in vivo* after infection by *Vibrio anguillarum* M3. Lett Appl Microbiol. 2010 Aug 26 (copy of abstract attached). Hu *et al.* teaches that "[a]ntigens identified in this [IVIAT] study are potential targets for drug and vaccine development and may be utilized as diagnostic agents." Hu *et al.*, Identification of *in vivo* induced

protein antigens of *Salmonella enterica* serovar Typhi during human infection. Sci China C Life Sci. (2009) 52:942-8 (copy of abstract attached). Jiao *et al.* teaches that "these results demonstrate that Eta21 [an IVIAT protein], especially that delivered by DH5alpha/pTAET21, is an effective vaccine candidate against *E. tarda* infection." Jiao *et al.*, Fish Shellfish Immunol. (2009) 27(5):633-8 (copy of abstract attached). Song *et al.* teach that "IVIAT has proven useful in identifying previously unknown *in vivo*-induced genes that are likely involved in virulence and are thus excellent candidates for use in diagnostic, and therapeutic strategies, including vaccine design." Song *et al.* Genes of periodontopathogens expressed during human disease. Ann Periodontol. (2002) 7(1):38-42 (copy of abstract attached).

6. Therefore, those of skill in the art have recognized that polynucleotides and the polypeptides expressed from the polynucleotides that are discovered using IVIAT methodologies of the invention are useful as vaccine targets and diagnostic targets.

7. Vaccine targets are known to those of skill in the art as candidate polynucleotides or polypeptide antigens expressed from the polynucleotides that have a potential to be useful as a vaccine. Diagnostic targets are known to those of skill in the art as candidate polynucleotides or polypeptide antigens expressed from the polynucleotides that have a potential to be useful as a diagnostic composition.

8. I declare that all statements made herein to my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 10/25/2010

Signed: _____
Dr. Martin Handfield

APPENDIX A

1. Screening of genes expressed in vivo after infection by Vibrio anguillarum M3.
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2. Use of in vivo-induced antigen technology (IVIAT) to identify virulence factors of Porphyromonas gingivalis.
Wallet SM, Chung J, Handfield M.
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3. Identification of a Novel Virulence-Related Gene in Streptococcus suis Type 2 Strains.
Zhang H, Fan H, Lu C.
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Lowry JE, Goodridge L, Vernati G, Fluegel AM, Edwards WH, Andrews GP.
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5. Identification of in vivo induced protein antigens of Salmonella enterica serovar Typhi during human infection.
Hu Y, Cong Y, Li S, Rao X, Wang G, Hu F.
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7. Identification and immunoprotective analysis of an in vivo-induced Edwardsiella tarda antigen.
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14. Identification of in vivo-induced bacterial protein antigens during human infection with Salmonella enterica serovar Typhi.
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